REMARKS

Status of the Claims

There are 116 originally filed claims in the application. Claims 17-25, 32-41, 62-66 and 72-76 were canceled without prejudice in an Amendment filed April 17, 2003. In the Supplemental Amendment filed April 30, 2003, Applicants re-introduced new claims 123-153 (corresponding the canceled claims 17-25, 32-41, 62-66 and 72-76) because the claims were inadvertently canceled.

Claims 26 and 118 are canceled without prejudice. New claims 154-175 directed to product-by-process for each lamotrigine polymorph are added in this Amendment per Examiner's suggestions in the May 27, 2003 Office Action. The new product-by-process claims recite X-ray diffraction data for each lamotrigine form. No new matter has been introduced as support can be found throughout the specification. Accordingly, the pending claims include claims 1-16, 27-31, 42-61, 67-71, 77-117 and 119-175.

Brief Summary of Background

Applicants submit the following brief summary of the characteristics of crystalline solid of an organic compound (including solvates of the crystalline solid form) that is relevant to the Applicants' invention of crystalline solid of lamotrigine.

Crystalline vs Amorphous Forms

Solids can exist in crystalline or amorphous form. Crystalline materials have defined structures, stoichiometric compositions, and melting points and are characterized by their chemical, thermal, electrical, optimal and mechanical properties. By contrast, amorphous materials have no clearly defined molecular structure and non long-range order, so their structure can be viewed as being similar to that of a frozen liquid but without the thermal fluctations observed in the liquid phase. As a result, amorphous materials exhibit the classical diffuse "halo" x-ray powder diffraction pattern rather than the sharp peaks observed in the pattern of a crystalline substance. ("Brittian[1]", pp. 208-209) (attachment 1)

Preparation of Crystalline Solid Form is Unpredictable

[1] Brittian, H.G., *Polymorphism in Pharmaceutical Solids* p. 205 (Marcel Dekker 1999)

There is a variety of ways to try to prepare new polymorphic forms, including: sublimation, crystallization from a single solvent, evaporation from a binary mixture, vapor diffusion, thermal treatment, crystallization from a melt, rapidly changing pH to precipitate acids and bases, thermal desolvation of crystalline solvates, growth in the presence of additives and grinding. ("Brittian", p.183) (attachment 2). None of these methods can be predicted in advance to yield a particular polymorph.

Often, when solvents are employed in the purification of new drug substances by recrystallization, it is observed that the isolated crystals include solvent molecules, either entrapped spaces in the lattice or interacting via hydrogen bonding or van der Waals force with molecules constituting the crystal lattice. ("Brittian", pp205-208) (attachment 3). Only about one third of organic compounds are capable of forming hydrates and other solvates. ("Brittian", pp. 128-29) (attachment 4). van der Sluis and Kroon found 1,274 different compounds with cocrystallized solvent in the Cambridge Crystallographic Database. Out of 46,460 total structures, they found 9,464 solvate structures, and 95% of these contained one of the 15 solvants. The most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry, but occasionally mixed solvate species are encountered. ("Brittian" pp. 206-208) (attachment 5). The manner in which water leaves a hydrate is also unpredictable. While some higher hydrates undergo stepwise dehydration with increased temperature, not all polyhydrates do so. ("Brittian", p. 66) (attachment 6). Erythromycin dihydrate loses both waters of crystallization simultaneously.

Examples like these of the unpredictability of the solid-state behavior of compounds underlie the repeated statements by authorities on solid state chemistry that the solid state forms that an organic compound can take cannot presently be predicted in advance. "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." ("Brittian", p.185) (attachment 7). With the advent of molecular modeling techniques for crystal growth prediction, interest has been generated in the computer prediction of polymorphism. The task is difficult because of the lacunae in our understanding of polymorph structure. There are no general rules that allow prediction of whether a compound will exhibit polymorphism.

Preparation of Polymorphic Forms

"In some instances, a compound of a given hydration state may crystallize in more than one form, so that the hydrates themselves exhibit polymorphism. ("Brittian", p. 203) (attachment 8). Polymorphic forms can be detected by a light microscopist as an interloper among crystals of another form. However, a single crystal of a new form does not come packaged with instructions how to prepare it.

"The microscopist can detect numerous polymorphic transformations, but the individual polymorphs often prove to be so unstable that they cannot be isolated by the usual methods. An excellent example of this is the work of Grieβer and Burger on etofylline. The authors identified five polymorphic forms by thermomicroscopy, but only stable Modification I could be obtained by recrystallization, even when seed crystals from the hot stage were used. Similarly, Kuhnert-Brandstatter, Burger, and Vollenklee described six polymorphic forms of piracetam, only three of which could be obtained by solvent recrystallization. All the others were found only by crystallization from the melt. What, then, is a careful investigator to do?" ("Brittian", p. 186) (attachment 9).

Characterization of Crystalline Solid of Organic Compound

Of all the methods available for the physical characterization of solid materials, it is generally agreed that crystallography, microscopy, thermal analysis, solubility studies, vibrational spectroscopy, and nuclear magnetic resonance are the most useful for the characterization of polymorphs and solvates. However, it cannot be overemphasized that the defining criterion for the existence of polymorphic types must always be a nonequivalenence of crystal structures. For compounds of pharmaceutical interest, this ordinarily implies that a nonequivalent x-ray powder diffraction pattern is observed for each suspected polymorphic variation. All other methodologies must be considered as sources of supporting and ancillary information; they cannot be taken as definitive proof for the existence of polymorphism by themselves alone. ("Brittan", pp.228-229) (attachment 10).

The x-ray crystallography technique, whether performed using single crystals or powdered solids, is concerned mainly with structural analysis and is therefore eminently suited for the characterization of polymorphs and solvates. An external examination of

crystals reveals that they often contain facets, and that well-formed crystals are completely bounded by flat surfaces. ("Brittan", p.229) (attachment 11)

In fact, most drug substances are obtained as microcrystalline powders, from which it is often fiendishly difficult to obtain crystallographically adequate crystals. Furthermore, during the most common compound is indeed of the desired structure. For these reasons, and to its inherent simplicity of performance, the technique of x-ray powder diffraction (XRPD) is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of polymorphs and solvates...The XRPD pattern will therefore consist of a series of peaks detected at characteristic scattering angles. These angles, and their relative intensities, can be correlated with the computed d-spacings to provide a full crystallographic characterization of the powdered sample. After indexing all the scattered lines, it is possible to derive unit cell dimensions from the powder pattern of the substance under analysis. For routine work, however, this latter analysis is not normally performed, and one typically compares the powder pattern of the analyte to that of reference materials to establish the polymorphic identity. Since every compound produce its own characteristic powder pattern owing to the unique crystallogrphy of its structure, powder x-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of an analyte. The USP general chapter on x-ray diffraction states that identity is established if the scattering angles of ten strongest reflections obtained for an analyte agree to within ± 0.2 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent. ("Brittan", pp. 235-236) (attachment 12).

Applicants' Invention

Applicants have discovered novel crystalline forms of lamotrigine and methods for preparing them. Further, Applicants have discovered distinct crystalline solid forms which have been designated as forms B, C, D, E, E1, F, H, J, K, L, M, N, O, P, Q, R, S, and U. Each form is characterized by XRPD and thermal analysis.

Lamotrigine crystal form isopropanolate has been reported and the crystallographic structure of lamotrigine methanolate is known. It is unknown if there exist other lamotrigine crystalline forms and their characteristics is presently unknown. Applicants' invention is directed to the discovery of many novel lamotrigine crystalline

forms. Using XRPD and thermal analysis, Applicants further characterized the following novel crystalline solid forms of lamotrigine:

forms B (monosolvate of DMF),
form C (sesquisolvate of DMF),
form D (2/3 solvate of DMF),
form E (2/3 methanolate),
form E1 (2/3 ethanolate),
form F (1/3 acetonate),
form H (monosolvate of ethanol),
form E1 (monosolvate of methanol),
form J (monosolvate of isopropanol),
form K (monosolvate of THF),
form L (monosolvate of acetone),
form M (monosolvate of DMA),
form N (monohydrate),
form O (monoethanolate),
form Q (monosolvate of isopropanol),
form R (monosolvate of methyl-isobutyl-ketone),
form S (anhydrous), and
form U (monosolvate of methyl teritary-butyl ether).

Substantive Arguments

Use of Common Name

Examiner rejects the use of common name lamotrigine. Applicants respectfully submit that the chemical name for lamotrigine is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine. Per Examiner's request, the common name of "lamotrigine" in all the pending claims has been replaced with the chemical name. Applicants believe that Examiner's rejection has been obviated.

Claims 151-153

For sake of clarity, Applicants address the Examiner's issues point-by-point. **First**, Applicants have now recited lamotrigine in its chemical name. To that end, the pending claims have been amended accordingly. **Second**, Examiner alleges that it is improper to refer to a figure (e.g., figure 15) within a claim. Applicants respectfully traverse the objection. It is generally not permissible to include in utility patent claims of an express reference to a drawing, however, such inclusion is permissible under limited circumstances. *Ex parte Fressola*, 27 USPQ2d 1608 (BPAI 1993). For example, the Board in *In Ex parte Gring and Mooi* has permitted reference to the drawing (a photomicrograph) which the applicants submitted pursuant to MPEP § 608.02. Accordingly, the Board permits "reference in a claim to a figure of an application drawing where such reference points out with

sufficient clarity which could be set forth **in words** only with prolixity and less clarity." (emphasis added) Here, a XRPD diffractogram can sufficiently provide clarity (with respect to the two-theta angles where peaks occur and the magnitude of the peaks) that words otherwise cannot. Accordingly, Applicants respectfully request the objection be withdrawn. **Third**, Applicants respectfully submit that claims 150 and 151 are not contradictory because claim 151 contains additional two (2) peaks in addition to those that have been recited in claim 150. **Fourth**, Applicants appreciate Examiner's suggestion to combine claims 124-128, but believe the present claims adequately claim the inventors' invention.

35 U.S.C. § 112, 2nd Paragraph

Examiner rejected claims 124-153 under 35 U.S.C.§ 112, 2nd paragraph. Applicants believe that use of chemical name and an alpha-numerical in describing a polymorph is conventional and standard practice that has been routinely found acceptable by the PTO. Applicants conducted a quick search in USPTO patent database with the search term "aclm/(polymorphic and form) and identified over a hundred issued US patents. US Pat. Nos. 6,538,134, 6,525,185 and 6,492,379 exemplify the use of a chemical name followed by an alpha-numerical in the claims. Applicants replace the common name of lamotrigine with its chemical name because the chemical name has the same meaning as the common name. There is no narrowing of claim scope. Applicants request the rejection be withdrawn.

Claims 92-93

Claims 92-93 stand rejected as inherently anticipated under 35 U.S.C. § 102 over Janes *et al.* [Acta. Cryst., (1989, C45, 129-132)] (hereinafter, Janes reference) which describes i) a lamotrigine methanol solvate (monoclinic P21/n) and ii) a form of lamotrigine crystallized from absolute ethanol (monoclinic space). There is simply no disclosure of any solvate of DMF (forms B, C, D), acetonate (forms F, L), isopropanol (forms J, Q), THF (form K), DMA (form M), hydrate (form N), methyl-isobutyl-ketone (forms R and U).

With respect to the claimed lamotrigine forms (e.g., forms B, C, D, F, J, K, L, M, N, P, Q, R, S and U) other than methanolate and ethanolate forms, there is no inherency because the preparation of these forms involves different organic solvents.

With respect to the methanolate and ethanolate forms (i.e, forms E, E1, H, and O), Applicants claim methanoate and ethanolate resulting from the disclosed method and

XRPD characterization data. Examiner has conceded that the Janes reference never expressly disclose the presently disclosed method and XRPD characterization data. Janes reference fails to disclose any method of preparing lamotrigine methonate; instead, it states "[s]ample provided by the Wellcome Research Laboratories, UK." (page 130, left column, lines 3-4). Janes reference also fails to disclose any method of preparing lamotrigine ethanolate. It simply states "[a] second form of lamotrigine has been crystallized from absolute ethanol..." (page 131, right column, 39-40). Janes reference is nothing more than a non-enabling disclosure.

Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich and Divigard*, 666 F.2d 578 (CCPA 1981). Anticipation by inherency requires that 1) the missing descriptive matter be "necessarily present" in the prior art reference and that 2) it would be so recognized by persons of ordinary skill in the art. *Continental Can Co. v. Monsanto Co.*, 948 .2d 1264 (Fed.Cir. 1991). When prior art fails to disclose a method for making a claimed compound, at the time the invention was made, it cannot be legally concluded that the compound itself is in the possession of the public. *Ashland Oil, Inc. v Delta Resins & Refractories, Inc.* 776 F.2d 281 (Fed. Cir. 1985).

As clearly can be seen from the present invention, different crystallization conditions (e.g., different solvent used, different temperature employed, stirring and filtering etc) indeed affect the outcome --- whether a particular lamotrigine crystalline form can be formed. Given the defective teaching by Janes reference, one skilled in the art cannot "necessarily flow" to lead to the claimed lamtorgrine form. Therefore, Janes reference fails to anticipate these claims by inherency. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C.§ 102 inherency rejection.

Claims 117-123

Examiner rejects claims 117-123 under 35 U.S.C. § 112, 2nd paragraph as alleging 1) not knowing what is being prepared; 2) heating step is part of prior art; 3) source of starting materials; and 4) identity of starting material.

Applicants have amended claim 117 that clearly indicates the source of starting material and the identity of the starting material; accordingly, one skill in the art

would know what is being prepared. Because these lamotrigine forms are novel and unobvious, therefore, there is no teaching in the prior art of heating these lamotrigine forms to obtain lamotrgine A. Applicants traverse the Examiner's rejection that "heating step is part of prior art." Applicants urge the Examiner to withdraw the rejection or to provide objective evidence of such a prior art.

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Applicants submit that the present invention is directed to novel crystalline solid forms of lamotrigine (designated as forms B, C, D, E, E1, F, H, J, K, L, M, N, O, P, Q, R, S and U), each crystalline form is characterized by unique XRPD spectra and/or thermogravimetric data. Examiner seems unpersuasive about the description of a new crystalline form. For background information, Applicants respectfully submit herewith a "**Brief Summary of Background**" which describes crystalline solid form of polymorphs and how they are characterized.

35 U.S.C. § 112, 2nd Paragraph

Claims 2-16 stand rejected under 35 U.S.C. § 112, 2nd paragraph. Applicants appreciate Examiner's suggestion to combine information of claims 124-128 in the same claim, but believe the present claims better claim the inventors' invention. The amended claims 124-153 are clear and precise and accordingly satisfy the 35 U.S.C.§ 112, 2nd paragraph requirement. Applicants request the rejection be withdrawn.

Claims 1-16 Rejection

Claims 1-16 stand rejected for reasons noted in the previous Office Action. Applicants maintain that the present novel lamotrigine forms are novel and unobvious. Applicants believe that the Responses filed on 4/17/2003 and 4/30/2003 have fully addressed the Examiner's rejection in previous Office Action and respectfully request the Examiner to reconsider withdrawn of the rejection.

Form E1

Claim 26 is canceled in this Amendment without prejudice. Form E1 is still in claims 129 and 133 because the originally filed claims 22-26 directed to crystalline solid form E1 were inadvertently canceled through a mistake without any deceptive intent on the Applicants' part. Claims 129-133 were re-introduced via the Supplemental Amendment filed

April 30, 2003. In this Amendment, claims 129-133 have been amended in accordance with the Examiner's suggestion.

Claims 27-31

Applicants amended claim 27 as suggested. Applicants respectfully submit that this crystalline form of lamotrigine is novel and unobvious as there is no prior art disclosing or suggesting/teaching the form.

Applicants respectfully submit that crystalline solid lamotrigine forms K, L, M, N, P, R, S and U are not in any prior art.

Claims 94-116

Applicants submit that these claims recite a method of preparing respective crystalline lamotrigine forms. Although the lamotrgine anhydrous is known, the process of preparing novel lamotrgine crystalline forms using lamotrogine anhydrous has not disclosed or suggested in the prior art.

Claims 1-16, 26-31, 42-61, 67-71, 77-93 and 124-153

Claims 1-16, 26-31, 42-61, 67-71, 77-93 and 124-153 stand rejected under 35 U.S.C. § 102 as the Examiner alleges that: 1) "no additional property is seen alleged"; 2) "no physical melting point different is seen alleged"; 3) "no utility variation is seen alleged"; 4) "no reason is seen established to not believe that the forms alleged are not inherent in the known material."

Applicants respectfully submit that the XRPD analysis represents the important tool in the study of polycrystalline materials and is eminently suited for the routine characterization of polymorphs and solvates (see above). The present application provides XRPD data which constitutes an adequate characterization of a particular crystalline solid alone. Also, TGA is provided. Applicants submit that the characterization data presented in the application is sufficient and there is no additional need for any other properties such as melting points or utility variation. Applicants respectfully submit that the present claimed crystalline solid forms do not exist in prior art.

Claims 1-16, 26-31, 42-61, 67-71, 77-93 and 124-153 stand rejected under 35 U.S.C. § 101 as the Examiner alleges that: 1) "are these forms stable on long standing?"; 2) "what industrial applicability do these form have, that the compounds that are known do not have?"; 3) "generally when something is allowed, it is better than the prior art at something. Is that present here?"

Applicants point Examiner's attention to page 13 of the present specification regarding issues raised by Examiner including industrial applicability. With respect to the issue of 35 U.S.C. § 101, Applicants submit that the present invention is directed to a new and useful compound that is useful as anti-epileptic drug. Applicants submit that 35 U.S.C. § 101 imposes no requirement that an invention be better than the prior art.

Structure of What is Being Claimed

Examiner rejected the claims as lacking the description of the structure of what is being claimed. Applicants traversed the Examiner's rejection. There is no statutory requirement that the structure of a crystalline solid form of a compound needs to be disclosed in order to secure allowance of claims that cover the crystalline solid form.

Applicants gratefully appreciate Examiner's suggestions with respect to product-by-process claims. Applicants therefore adopted Examiner's suggestion and present new claims 154-175 directed to detailed product-by-process with X-ray diffraction data for each polymorph forms claimed.

Applicants believe that the pending claims are free of prior art and patentable and allowance of these claims is respectfully requested. The Examiner can reach undersigned at (212) 908-6018 when this application is taken up for further action.

Respectfully submitted,
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